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(54) Pharmaceutical formulation containing diphenhydramine, talc, calamine and oat extract in an emulsified base and uses thereof.

(57) It comprises: 0.25-2.0% diphenhydramine hydrochloride or base; 0.1-10.0% colloidal oat extract; 0.05%-10% calamine or zinc oxide; 1-20% talc, 0.1-10% emulsifying agent; and, optionally, one or more ingredients selected among viscosity modifying agents, consistency regulators, water-repellent protectors, preservatives, emollients, antioxidants, chelating agents, lipidic substances and biocompatible polymers.

Use in topical treatment of allergic type dermatosis accompanied by itching and/or pain.

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FIELD OF THE INVENTION

The present invention refers to an antiallergic, hydrophilous, dermatological topical pharmaceutical preparation useful to treat dermatitis, exanthemas, insect bites, rashes, eczemas, urticaria and minor skin irritations accompanied by itching and/or pain.

Specifically, the preparation contains diphenhydramine hydrochloride in an emulsified vehicle that includes oat extract, in an emulsified base, for topical dermatological use.

PRIOR ART OF THE INVENTION

The topical antihistamines used to treat allergic-type dermatosis accompanied by itching and/or pain are included alone or combined with other active components, generally in the form of a solution, fluid or semisolid emulsion, gel or powder diluted in talc.

In the case of solutions, emulsions or gels, the topical antihistamines are never combined with oat flour (colloidal oat extract) or hydrated magnesium silicate (talc), ingredients which appear in the present invention and that contribute to alleviate itching, aside from reducing inflammation and facilitate gentle spreading of the preparation over damaged areas, aspects to be well kept in mind in skin affections that are accompanied by itching and/or pain.

Antihistamines diluted in talc to be sprinkled over the lesion are not associated either with an oat derivative. Besides, in this type of product there are risks of irregular distribution and of producing a cloud of powder that can cause respiratory disorders after inhalation thereof.

DETAILED DESCRIPTION OF THE INVENTION

The present invention refers to an antiallergic-antipruritic topical pharmaceutical preparation that contains an antihistamine combined with oat flour (colloidal oat extract) in an emulsified vehicle that also includes calamine and talc or other drying, softening, emollient or protective ingredients.

Oat flour (colloidal oat extract) is a substance with absorption capacity and that provides the skin with emollience.

Including calamine in the composition allows the product to be given its astringent and decongestant power.

To reinforce the properties of the active principle it is very useful to add softeners, protective agents, astringents and decongestants. Thus, it is particularly interesting to add talc, a hydrated magnesium silicate, well known and amply used as a softener and protective agent, in different dermatosis, due to its adherence and soft touch.

Talc is normally used in powder form in suitable containers to sprinkle the same, but this form of application has some inconveniences, such as for example irregular distribution and the formation of a cloud of powder that is easy to inhale and that can cause problems in the respiratory tract, particularly in children.

Upon being included in the emulsified vehicle of the present invention, talc is easily distributed over the surface to be treated without producing dust.

Including an antihistamine such as diphenhydramine hydrochloride, amply used due to its antiallergic and antipruritic properties, to active bases such as those indicated reinforces the soothing power of said active principle due to the coolness given to the aqueous emulsified vehicle and due to the softening, emollient and astringent action of the combination of the rest of the cited components.

The compositions of the present invention also include other ingredients normally used in dermatological topical preparations, such as for example, viscosity modifying agents, emulsifying agents, consistency regulators, protective agents, preservatives, emollients, antioxidants and chelating agents.

The compositions of the present invention can include substances used in microencapsulation, such as for example biocompatible polymers and different lipidic substances.

Including any representative of the above mentioned groups of compounds depends on the characteristics to be given to the final preparations. Choosing one compound or another depends on the physical, physicochemical and chemical characteristics of the rest of the components of the formulation in order to obtain a stable, well tolerated and therapeutically effective preparation.

Carboxyvinyl polymers, cellulose derivatives and gums, among others, can be cited as viscosity modifying agents. These compounds are normally used at some levels between 0.01 and 0.5%.

Keto-stearyl alcohol combined with non-ionic or anionic emulsifying agents, polyethyleneglycol stearate, polyglycol esters and polyoxyethylenesorbitan stearates, oleates or laurates can be cited among emulsifying agents. These compounds are normally used at some levels between 0.1 and 10%.

Cetyl alcohol, stearyl alcohol, keto-stearyl alcohol and stearic acid, among others, can be included as consistency regulators. The most normal levels of these compounds vary between 0.25 and 5%.

Dimethicones and cyclomethicones, among others, can be included as protective ingredients. These compounds are normally used at some levels between 0.1 and 10%.

Parabens, solutions of parabens in phenoxyethanol (Phenonip), chloroisothiazolinone and methylchloroisothiazolinone solution (Kathon CG), imidazolidinylurea (Germall 115), among others, can be cited as preservatives. These compounds are typically used at some levels between 0.01 and 0.6% (Kathon CG as a maximum of 0.15%.)

Lanolin and derivatives, glycerol and petrolate, among others, can be cited as emollients. These compounds are typically used at some levels between 0.05 and 10%.

BHT, BHA, tocopherol or esters thereof and sodium sulfite, among others can be included as antioxidants. These compounds are normally used at some levels between 0.01 and 2%.

As chelating agents, we can cite citric acid and disodium salt of ethylenediaminetetraacetic acid, EDTA. These compounds are included to improve the action of the preservatives. These compounds are typically used at some levels between 0.01 and 2%.

A polyacrylic, polylactic, polyglycol derivative, a polylactic-glycol copolymer, a polyanhydride, a polyamide, a poly(alpha-amino acid), cellulose polymers, natural polymers, or a mixture of two or more of the cited compounds can be included as biocompatible polymers. These compounds are typically used at some levels between 0.1 and 5.0%.

Coconut oil, ethoxylated oleic glycerides, diethyleneglycol monoethyl ether, C_8-C_{10} ethoxylated glycerides, phospholipids, natural oils or petroleum derivatives or a mixture of several of them can be used as lipidic substances. These compounds are normally used at some levels between 0.01 and 20%.

In accordance with the present invention, the resulting formulation includes between 0.25 and 2% diphenhydramine hydrochloride and between 0.1 and 10% of a colloidal oat extract in en emulsified vehicle that also includes, between 0.05 and 10% calamine or zinc oxide and between 1 and 10% talc or other drying, softening, emollient or protective ingredients.

The amount of preparation that can be administered to the patient depends on his age as well as his general state of health and on the severity and type of disease suffered from. Though the doctor is to establish the dosage, it is recommended that the application of the formulations included in the present invention be done 2 to 4 times a day, spreading the preparation as a fine layer.

The formulations included in the present invention can be contained in the containers normally used for this type of preparation, depending on the type of resulting pharmaceutical form.

EMBODIMENTS OF THE INVENTION

The following formulations are given as representative examples of the compositions included in the present invention and they must not be considered as limitations of the scope of the same.

EXAMPLE Nº 1. Fluid emulsion

Substance	Amounts per 100 g
Carbomer 940	0.17 g.
Phenonip	0.60 g.
Colloidal oat extract	5.00 g.
Talc	10.00 g.
Keto-stearyl alcohol	0.60 g.
Cyclomethicone	0.50 g.
Dimethicone	0.50 g.
Polyoxyethylenated cetyl emulsifying agent	2.50 g.
Triethanolamine	0.20 g.
Ethoxylated lanolin	0.40 g.
Kathon CG	0.10 g.
Calamine	2.00 g.
Diphenhydramine hydrochloride	1.00 g.
Purified water q.s.	100.00 g.

Preparation method

Aqueous phase

Place in a suitable container the purified water, except the amount needed to dissolve the diphenhydramine hydrochloride, add Carbomer 940 and Phenonip (50% of the total amount) and stir until swelling of the Carbomer 940. Then add, with stirring, the colloidal oat extract and the talc and heat to 70º C.

Fatty phase

In a separate container, melt and stir until homonegeity keto-stearyl alcohol, cyclomethicone, dimethicone, emulsifying agent and the rest of the Phenonip. Heat to 70º C.

Preparation of the emulsion

The two phases at 70º C, add the fatty phase to the aqueous phase with stirring and once the mixture is homogeneous, add the triethanolamine and the ethoxylated lanolin, maintaining the stirring.

Refrigerate and add, at 40º C, the Kathon CG and then the calamine. Finally, once the suspension is homogenous and the temperature is about 30º C add the diphenhydramine hydrochloride solution in twice its weight of water.

EXAMPLE Nº 2. Fluid emulsion

Substance	Amounts per 100 g.
Palmito-polyglycol stearate	7.00 g.
Stearic acid	1.00 g.
Mono,di palmito-glyceryl stearate	1.00 g.
2-octyl dodecyl myristate	5.00 g.
Borage oil	0.50 g.
Avocado oil	3.00 g.
Alpha-bisabolol	0.10 g.
Tocopherol acetate	1.00 g.
Panthenol	1.00 g.
Carbomer 941	0.10 g.
Triethanolamine	0.20 g.
Kathon CG	0.10 g.
Antioxidant	0.10 g.
Colloidal oat extract	5.00 g.
Talc	10.00 g.
Calamine	2.00 g.
Diphenhydramine hydrochloride	1.00 g.
Perfume	0.20 g.
Purified water q.s.	100.00 g.

Preparation method

Aqueous phase

In a suitable container, swell in purified water, except the amount needed to dissolve the diphenhydramine hydrochloride, Carbomer 941, add the panthenol and homogenize. Add the colloidal oat extract and the talc. Heat to 70º C.

Fatty phase

In a separate container, melt and homogenize palmito-polyglycol stearate, stearic acid, mono, di palmito-glycerol stearate, 2-octyl dodecyl myristate, borage oil, avocado oil, alpha-bisabolol, tocopherol acetate and antioxidant. Heat to 70º C.

Preparation of the emulsion

The two phases at 70º C, add the fatty phase to the aqueous phase with stirring and once the mixture is homogeneous, add the triethanolamine. Keep stirring. Refrigerate and add, at 40º C, Kathon CG and then the calamine. Finally, once the suspension is homogeneous and the temperature is about 30º C, add the diphenhydramine hydrochloride solution in twice its weight of water and the perfume.

EXAMPLE Nº 3. Semisolid emulsion

Substance	Amounts per 100 g.
Palmito-polyglycol stearate	12.00 g.
Stearic acid	1.00 g.
Moni, di palmito-glyceryl stearate	2.00 g.
2-octyl dodecyl myristate	10.00 g.
Borage oil	0.50 g.
Alpha-bisabolol	0.10 g.
Tocopherol acetate	3.00 g.
Panthenol	1.00 g.
Kathon CG	0.10 g.
Colloidal oat extract	5.00 g.
Talc	10.00 g.
Calamine	2.00 g.
Diphenhydramine hydrochloride	1.00 g.
Perfume	0.20 g.
Purified water q.s.	100.00 g.

Preparation method

Place in a suitable container the purified water, except the amount needed to dissolve the diphenhydramine hydrochloride, add the panthenol and homogenize. Add the colloidal oat extract and the talc. Heat to 70º C.

Fatty phase

In a separate container, melt and homogenize the palmito-polyglycol stearate, stearic acid, mono, di-palmito-glyceryl stearate, 2-octyl dodecyl myristate, borage oil, alpha-bisabolol and tocopherol acetate. Heat to 70º C.

Preparation of the emulsion

The two phases at 70º C, add the fatty phase to the aqueous phase with stirring and keep stirring.

Refrigerate and add, at 40º C, the Kathon CG and then the calamine. Finally, once the suspension is homogenous and the temperature is about 30º C, add the diphenhydramine hydrochloride solution in twice its weight in water and the perfume.

EXAMPLE Nº 4. Fluid emulsion

Substance	Amounts per 100 g.
Carbomer 940	0.17 g.
Phenonip	0.60 g.
Colloidal oat extract	5.00 g.
Talc	10.00 g.
Keto-stearyl alcohol	0.60 g.
Cyclomethicone	0.50 g.
Dimethicone	0.50 g.
Polyoxyethylenated cetyl emulsifying agent	2.50 g.
Triethanolamine	0.20 g.
Ethoxylated lanolin	0.40 g.
Kathon CG	0.10 g.
Calamine	2.00 g.
Colloidal suspension 2% of nanocapsules or nanospheres of diphenhydramine	25.00 ml.
Purified water q.s.	100.00 g.

Preparation method

Aqueous phase

Place in a suitable container the purified water, add the Carbomer 940 and the Phenonip (50 % of the total amount) and stir until swelling of the Carbomer 940. Then add, with stirring, the colloidal oat extract and the talc and heat to 70º C.

Fatty phase

In a separate container, melt and stir to homogeneity keto-stearyl alcohol, cyclomethicone, dimethicone, emulsifying agent and the rest of the Phenonip. Heat to 70º C.

Preparation of the emulsion

The two phases at 70º C, add the fatty phase to the aqueous phase with stirring and once the mixture is homogeneous, add the triethanolamine and the ethoxylated lanolin. Keep stirring.

Refrigerate and add, at 40º C, the Kathon CG and then the calamine. Finally, once the suspension is homogeneous and the temperature is about 30º C, add the colloidal suspension 2% of nanocapsules or nanospheres of diphenhydramine.

Claims

1. Pharmaceutical formulation containing diphenhydramine, talc, calamine and oat extract, in an emulsified base, for dermatological use, characterized in that it comprises:
   - 0.25-2.0% dephenhydramine hydrochloride or base,
   - 0.1-10.0% colloidal oat extract,
   - 0.5-10% calamine or zinc oxide,
   - 1-20% talc
   - 0.1-10% emulsifying agent,
   - optionally, 0.01-0.5% viscosity modifying agent,
   - optionally, 0.25-5.0% consistency regulator,
   - optionally, 0.1-10% water-repellent protector,
   - optionally, 0.01-0.6% preservative,
   - optionally, 0.05-10.0% emollient,
   - optionally, 0.01-2.0% antioxidant,
   - optionally, 0.01-2.0% chelating agent,

- optionally, 0.01-20% lipidic substances that take part in the microencapsulation of the diphenhydramine inf the formulation,
- optionally, 0.1-5.0% biocompatible polymers that take part in the microencapsulation of the diphenhydramine of the formulation.

2. A formulation, according to claim 1, characterized in that the emulsifying agent is selected from the group comprised of polyoxyethylenated cetyl alcohol, sodium cetyl-sulfate, sodium cetyl-stearyl sulfate, palmito-glycol stearate, polyethyleneglycol stearate, polyglycol ethers and polyoxyethylenated sorbitan esters.

3. A formulation, according to claim 1, characterized in that the viscosity modifying agent is selected from the group comprised of carboxyvinyl polymer, metylcellulose, carboxymetnylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose and gum.

4. A formulation, according to claim 1, characterized in that the consistency regulator is selected from the group comprised of cetyl alcohol, stearyl alcohol, keto-stearyl alcohol and stearic acid, as well as by any of the emulsifying agents cited in claim 2.

5. A formulation according to claim 1, characterized in that the protector is selected from the group comprised of dimethicones and cyclomethicones.

6. A formulation according to claim 1, characterized in that the preservative is selected from the group comprise of paraban, solutions of paraben in phenoxyethanol (Phenonip), chloroisothiazolinone and methylchloroisothiazolinone solution (Kathon CG) and imidazolidinylurea.

7. A formulation according to claim 1, characterized in that the emollient is selected from the group comprised of lanolin and derivatives, glycerol and petrolate.

8. A formulation according to claim 1, characterized in that the antioxidant is selected from the grupp comprised of BHT, BHA, tocopherol (or esters thereof) and sodium sulfite.

9. A formulation according to claim 1, characterized in that the chelating agent is selected from the group comprised of citric acid and disodium salt of ethylenediamine tetraacetic acid (EDTA.)

10. A formulation according to claim 1, characterized in that the excipient is selected from among agents that allow the diphenyhydramine of the formulation to be microencapsulated, such as the lipidic substances (coconot oil, ethoxylated oleic glyceride, diethyeleneglycol monoethyl ether, C_8-C_{10} ethoxylated glyceride, phospholipids, natural oils or petroleum derivatives or a mixture of several of them) and biocompatible polymers (polyacrylic, polylactic, polyglycol derivative, a polylactic-glycol copolymer, a polyanhydride, a polyamide, a poly-alpha-amino acid, cellulose polymers, natural polymers or a mixture of two or more of the cited compounds.

11. Use of the formulations of above claims 1 to 10 for topical treatment of allergic-type dermatosis accompanied by itching and/or pain.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 94 20 1878

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Y	US-A-4 929 619 (STEVEN T. BLACKMAN) * column 2, line 1 - column 4, line 16; examples 1-15 *	1-11	A61K31/135 A61K47/00
Y	FED.REGIST., vol.55, no.119, 1990 pages 25204 - 25232 JAMES S. BENSON 'skin protectant drug products for over-the -counter human use' * page 25214, left column - right column * * page 25223, right column - page 25224, right column * * page 25226, left column - right column * * page 25232 *	1-11	
Y	US-A-4 014 995 (ANGELO L. JULIANO) * the whole document *	1-11	
Y	US-A-4 018 918 (DONALD E. AYER) * column 11, line 3 - column 12, line 44 *	1-11	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)
A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	9 February 1995	Tzschoppe, D

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

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